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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/770,689	01/29/2001	Chunhua Yan	CL001079	5442

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EXAMINER	
CANELLA, KAREN A	

ART UNIT	PAPER NUMBER
1642	11

DATE MAILED: 07/16/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/770,689	Yan et al
Examiner	**Art Unit**
Karen Canella	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3 months* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____.

2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *4, 8, 9, 13, and 24-29* is/are pending in the application.

4a) Of the above, claim(s) *13* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *4, 8, 9, and 24-29* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☒ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on *Jan 29, 2001* is/are a) ☐ accepted or b) ☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Acknowledgment is made of applicant's election with traverse of Group III, drawn to isolated nucleic acids which encode SEQ ID NO:2 or a fragment of SEQ ID NO:2, isolated nucleic acids which hybridize to the complementary strand of SEQ ID NO:1 or SEQ ID NO:3, isolated nucleic acids comprising variants of SEQ ID NO:1 or SEQ ID NO:3, vectors, host cells and the recombinant expression of SEQ ID NO:2. The traversal is on the grounds that the inclusion of claim 13, drawn to a method of detecting the claimed isolated nucleic acids, would not unduly burden the examiner. This has been considered but not found persuasive. The nucleic acids of elected Group III are related to the method of claim 13 as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the nucleic acids of Group III can be used to make the a non-human transgenic animal. Applicant argues that there is no additional burden associated with the examination of the method claim in addition to the product claims, as a search for the product would cover methods of using the product. This has been considered, but not found persuasive. The claims of Groups III and VI are classified differently, necessitating different searches in the U.S. Patent shoes. The classification of subject matter is merely one indication of the burdensome nature of the search involved. The literature search, particularly relevant in this art, is not co-extensive and is much more important in evaluating the burden of search. Further, the searches and patentability issues are not co-extensive, as the method claims rely on oligonucleotides as small as 20 contiguous nucleotides, in contrast to the product claims which are drawn to polynucleotides comprising cDNA and genomic sequences. Clearly different searches and issues are involved in the examination of each group.

However, the policies set forth in the Commissioner's Notice of February 28, 1996 published on March 26, 1996 at 1184 O.G. 86 will be followed. Method claims limited to the

scope of the allowable product claims will be rejoined and examined at the time the product claims are indicated as being allowable.

For these reasons the restriction requirement is deemed to be proper and is adhered to. The requirement is therefore made FINAL.

2. Claims 1-3, 5-7, 10-12 and 14-23 have been canceled. Claims 24-29 have been added. Claims 4, 8, 9, 13 and 24-29 are pending. Claim 13, drawn to a non-elected invention, is withdrawn from consideration. Claims 4, 8, 9 and 24-29 are examined on the merits.

3. Please note that the preliminary amendment filed May 22, 2002 has not been entered. Alterations to the Drawings cannot be directed into the specification by amendment. New drawings would be required to introduce the proposed amendments.

Specification

4. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code on page 13. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

5. The specification is objected to as not complying with 1.821(d) of the Sequence Rules and Regulations. Pages 3 and 4 contain amino acid sequences without an assigned identifier as required by the Sequence Rules and Regulations. Appropriate correction is required.

Claim Rejections - 35 USC § 101

6. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

7. Claims 4, 8, 9 and 24-29 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific, substantial, credible asserted utility or a well-established utility.

Claims 4, 8, 9 and 24-29 are drawn to isolated nucleic acids which encode the ras-like protein of the instant invention (SEQ ID NO:2). The specification discloses that the instant ras-like protein is related to the Nadrin protein which is a neuron-specific, developmentally regulated GTPase-activating protein that is important in regulating calcium-dependent exocytosis (page 5, lines 8-10). The specification asserts that the disclosed novel human ras-like protein is useful in the diagnosis, prevention and treatment of inflammation and disorders associated with cell proliferation and apoptosis (page 5, lines 19-22). The specification asserts that said ras-like protein is useful in assays such as high throughput screening to determine the biological activity of the protein, as a reagent in assays to quantitatively determine levels of the protein in biological fluids, and as markers for tissues in which the protein is preferentially expressed, either constitutively or at a particular stage of development, tissue differentiation or disease state. The specification asserts that the ras-like protein can be used to elicit an immune response or to raise antibodies, or to identify a ligand binding partner so as to develop a system to identify inhibitors of the binding interaction (page 17, lines 12-23).

The asserted utilities are not considered to be specific and substantial because the specification fails to disclose any particular function or biological significance for the ras-like protein of the instant invention. The use of said ras-like protein as a reagent to identify the biological activity of the protein, such as in a high throughput analysis, or in the raising of antibodies to detect the expression of the protein itself, or in assays designed to establish a binding partner for the claimed protein represents an experimental use of the protein which is part of the act of invention, and until it has been undertaken, applicant's claimed invention is incomplete.

The DNA of the instant invention and the protein encoded thereby are compounds which share some structural similarity to the Nadrin protein which is a neuron-specific, developmentally regulated GTPase-activating protein that is important in regulating calcium-dependent exocytosis (page 5, lines 8-10). In contrast, the ras-like protein of the instant invention was found by PCR to be expressed in human lymphocytes (figure 1). Further the specification discloses that "It is thought that Nadrin induces cortical actin filament reorganization; cortical actin filaments act as a cortical barrier and must be reorganized for docking and fusion of synaptic vesicles with plasma membranes". Thus, it is clear that one cannot anticipate the function of the ras-like protein of the instant invention, as the expression pattern includes lymphocytic cells in contrast to neurons, and the relevance of the reorganization of cortical actin filaments in lymphocytes is not suggested by the specification or any art of record.

Further, there is no apparent nexus between the asserted utilities of the diagnosis, prevention and treatment of inflammation and disorders associated with cell proliferation and apoptosis (page 5, lines 19-22) and the proposed molecular function of the instant ras-like protein which is related to the Nadrin polypeptide, said polypeptide a putative reorganizer of cortical actin fibers.

The specification further asserts that these potential uses are based primarily on the source of the protein as well as the class/action of the protein (page 17, lines 29-30). The specification states that "Experimental data as provided in figure 1 indicates that the ras-like proteins of the present invention are expressed in humans in teratocarcinomas (including neuronal teratocarcinomas) umbilical vein endothelial cells, iris, breast tissue, leiomas, uterus, kidney renal carcinoma (ascites), uterus leiosarcomas and fetal heart as indicated by virtual northern blot analysis. In addition, PCR-based tissue screening panels indicates expression in human leukocytes." (Page 18, last paragraph). Virtual northern blot data put forth in figure 1 indicate that a BLAST database search of EST sequences hit on Accession Numbers gi:

10993873, 11003732, 12040806, 10948137, 11303345, 7933255, 10332226, 11643637, 10348166, 4753575. Firstly, the claimed cDNA sequence of SEQ ID NO:1 consists of 3201 nucleotide residues. A data base hit with a EST sequence consisting of several hundred nucleotides does not guarantee that the claimed sequence of 3201 nucleotides is represented by that EST. Secondly, on examination of the annotations associated with each of the Accession Numbers it is noted that none of the EST sequuences were derived from subtracted libraries. Thus, it cannot be ascertained if the EST of the teratocarcinomas are present in the corresponding normal tissues, or if the EST of the kidney renal sarcoma was present in normal renal cells. Furthermore, it appears that the EST of the uterus leiomyosarcoma could be a tissue specific sequence as it was also found in uterine tissue. It is well known in the art that one cannot rely on a single hit in an EST database to establish the expression pattern of a gene. For instance, Yerushalmi et al (Gene, 2001, vol. 265, pp. 55-60) teach that the gene for ERGL was indicated to be expressed exclusively in the prostate by EST database searching, however, Northern blot hybridization indicated that the gene was also expressed in cardiac atrium, salivary gland, spleen and selective cells in the CNS. In contrast, Caillou et al (Journal of Clinical Endocrinology and Metabolism, 2001, Vol. 86, pp. 3351-3351) reports that Northern blot analysis of different human tissues demonstrated that the LNOX gene was expressed only in the thyroid gland, while blast analysis of EST sequences indicate that the LNOX gene is expressed in non-thyroid tissues. Furthermore, Conklin et al (Briefings in Bioinformatics, 2000, vol. 1, pp. 93-99) teach that the mining of EST databases using only a single member of a protein superfamily is prone to false positive hits as some proteins contain common domains (page 95, under the heading "Pruning the False Positives"). Thus, as stated above, a single hit in an EST database is not a guarantee that the full length nucleic acid of the instant invention is represented by that hit. It is also noteworthy that another ras-like protein was identified in teratocarcinoma cells by Drivas et al (Identification of Novel ras family genes in a human teratocarcinoma cell line by oligonucleotide screening" In:The ras-Superfamily of GTPases, Lacal and McCormick, Eds., 1993, pages 329-

347). However, this ras-like protein was found to be predominantly located in the nuclei of primate cells and not a specific marker for teratocarcinoma (page 343). This data serves to demonstrate that a database hit in an EST library does not establish either an expression pattern for a gene or a function for the encoded protein. If a molecule is to be used as a surrogate for a disease state, some disease state must be identified in some way with the molecule. There must be some expression pattern that would allow the claimed polynucleotide to be used in a diagnostic manner. Many proteins are expressed in normal tissues and diseased tissues. Therefore, one needs to know, e.g., that the claimed polynucleotide is either present only in cancer tissue to the exclusion of normal tissue or is expressed in higher levels in diseased tissue compared to normal tissue. Evidence of a differential expression might serve as a basis for use of the claimed polynucleotide as a diagnostic for a disease. However, in the absence of any disclosed relationship between the claimed polynucleotide or the protein that is encoded thereby and any disease or disorder and the lack of any correlation between the claimed polynucleotide or the encoded protein with any known disease or disorder, any information obtained from an expression profile would only serve as the basis for further research on the observation itself. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner*, 148 USPQ at 696. The disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. §101.

The instant situation is directly analogous to that which was addressed in *Brenner v. Manson*, 148 U.S.P.Q. 689 (1966), in which a novel compound which was structurally analogous to other compounds which were known to possess anti-tumor activity was alleged to be potentially useful as an anti-tumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 U.S.C. §101, which

requires that an invention must have either an immediately apparent or fully disclosed "real world" utility. The court held that:

> The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. . . . [u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field. . . . a patent is not a hunting license. . . .[i]t is not a reward for the search, but compensation for its successful conclusion.

The instant claims are drawn to a protein of as yet undetermined function or biological significance. There is no evidence of record or any line of reasoning that would support a conclusion that the ras-like protein of the instant application was, as of the filing date, useful for the diagnosis, prevention and treatment of inflammation and disorders associated with cell proliferation and apoptosis (page 5, lines 19-22). Until some actual and specific significance can be attributed to the protein identified in the specification as SEQ ID NO:2, or the gene encoding it, one of ordinary skill in the art would be required to perform additional experimentation in order to determine how to use the claimed invention. Such a use has been determined by the courts to be a utility which, alone, does not support patentability. Since the instant specification does not disclose a credible "real world" use for the ras-like protein of the instant invention, then the claimed invention as disclosed does not meet the requirements of 35 U.S.C. §101 as being useful.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 4, 8, 9 and 24-29 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific, substantial asserted utility or a well-established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

10. All claims are rejected.

Conclusion

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella

Karen A. Canella, Ph.D.

Patent Examiner, Group 1642

July 15, 2002